REMARKS

Claims 1-15, 22-29, 34-41, 43-45, and 47-54 are now pending. Claims 2, 3, 5, 6, 44 and 51 are amended to more particularly state the Applicants' invention, and are referred to in a Supplementary Reissue Declaration By Assignee. The following are also provided on pages 10-25 of this Response: (1) a listing of all amended claims showing the amendments cumulative to date relative to the original patent; (2) a listing of the amendments to the specification cumulative to date relative to the original patent; and (3) a listing of all the claims reflecting all amendments to date.

Applicants further provide herewith the Fasick Declaration, which relates to some laboratory observations recently made by Assignee.

A number of rejections and objections have been raised against the claims and the Reissue Declaration. For reasons set forth in detail below, these rejections and objections should be removed and the claims should be allowed to issue.

1. The Fasick Declaration

Attorneys for Applicants were recently contacted by persons associated with the assignee of this reissue application, International Bioimmune Sciences, Inc. ("IBS"), with regard to laboratory results which they believed to be anomalous involving the claimed murine antibodies. Part of the basis for this reissue application is the discovery that the original murine hybridoma deposits made in the prosecution of United States Patent No. 5,688,657 ("the '657 patent") were not correct. In the experiments brought to Attorney for Applicants Kole's attention, murine monoclonal antibody 31.1 produced by hybridoma cells deposited for this reissue application did not react with the expected (~70 kDa) sized protein in a a tumor antigen sample believed to be a preparation according to Hollinshead et al., 1985, Cancer 56:480-489 ("Hollinshead"), but rather reacted with a smaller protein (~43 kDa). An older antibody sample *did* react with a ~70 kDa sized protein. Since the immunogen used in the '657 patent was prepared by a method that included pooled colon carcinoma membranes prepared according to the method of Hollinshead, the IBS persons were concerned whether this was inconsistent with what would be expected properties of murine antibody 31.1, and whether these

results would raise a question regarding whether the correct hybridoma was deposited in this reissue application.

Attorney for Applicant Kole discussed this matter with Dr. Jeffrey Fasick of IBS, and his Declaration is enclosed herewith. Dr. Fasick states, at paragraph 10 of the Fasick Declaration:

> The fact that the Hollinshead TAA vaccine in the IBS freezer does not react with monoclonal antibodies covered in the '657 patent may be explained, in my opinion, by the fact that even though the protocols used to prepare immunogen were presumably similar, they were not necessarily the same; further, I believe that the tumor sources were not the same.

Further experiments are ongoing to address this issue, both for the 31.1 monoclonal antibodies and murine monoclonal antibody 33.28. Dr. Fasick is currently traveling and was unable to execute the Declaration, which is submitted unsigned. A signed version of the Declaration will be submitted promptly.

2. <u>The Reissue Declaration Is Not Defective</u>

The Examiner contends that the Reissue Declaration is defective because:

> it does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

Applicants assert that the Reissue Declaration submitted on November 5, 2004 is not defective because it makes the required representation. Applicants invite the Examiner's attention to the "Reissue Declaration by Assignee" at the bottom of page 5, which states as follows:

> IBS has reviewed and understands the amendments to the specification and claims of the '657 patent set forth in the RESPONSE submitted herewith, which, among other things, (1) now recite the new ATCC accession numbers of the hybridoma cells deposited during the pendency of this reissue application; (2)focus the claims on monoclonal antibodies 31.1 and 33.28 and chimeric antibody Chi #1, antibodies that competitively inhibit the binding of these specific antibodies to their target

antigens, and antibodies directed against the target antigens defined by these specific antibodies; (3) correct the erroneous statements relating to antigen specificity and purity of antigen in a sample; and (4) correct various typographical errors.

Every error in the patent which is corrected in the present reissue application, and is not covered by a prior oath/declaration submitted in this application, arose without any deceptive intention.

The Supplementary Reissue Declaration by Assignee submitted herewith makes the same representation, also at the bottom of page 5. Because the Reissue Declaration by Assignee and the Supplementary Reissue Declaration by Assignee make the required representation, it is requested that this objection, and any rejections of claims based on the objection, be withdrawn.

2. The Claims Cover Statutory Subject Matter

Claims 2, 5, 6, 51 and 53 are rejected under 35 U.S.C. §101 because, according to the Examiner, the claims do not sufficiently distinguish over antibodies as they exist in nature. The Examiner states that amending the claims to refer to an "isolated" of "purified" antibody would obviate the rejection.

Claims 2, 5 and 51 are amended to provide that the antibodies are purified. This amendment is acknowledged in the Supplementary Reissue Declaration by Assignee submitted herewith. Accordingly (and as claims 6 and 53 are dependent on claims 5 and 51, respectively) the rejection should be withdrawn.

3. The Claims Are Not Indefinite

Claims 3, 6 and 44 are rejected under 35 U.S.C. §112 as being indefinite for reciting a molecular weight without reciting how that molecular weight was determined.

Claims 3, 6 and 44 are amended to provide that the molecular weight was determined by gradient polyacrylamide gel electrophoresis, as provided in Example 1 of the instant specification. This amendment is acknowledged in the Supplementary

Reissue Declaration by Assignee submitted herewith. Accordingly, the rejection should be withdrawn.

4. The Amended Claims Are Not Anticipated

A. By Herlyn

Claims 5, 8-10, 13, 23 and 51-52 are rejected under 35 U.S.C. §102(b) as anticipated by Herlyn et al., 1979, Proc. Natl. Acad. Sci. U.S.A. 76:1138 ("Herlyn") and as evidenced by Koprowski et al., 1977, Proc. Natl. Acad. Sci. U.S.A. 74:2985-2988 ("Koprowski") because, according to the Examiner, Herlyn teaches antibodies to antigens from colon carcinoma cells which can be radiolabeled (according to Koprowski, with ^{125}I) and used for radioimmunoassay. The Examiner states:

> One of ordinary skill in the art would reasonably conclude that Herlyn's antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Herlyn have produced hybridomas that secrete antibodies that are identical to the claimed antibody.

The Examiner places the burden of proof on Applicants to show a distinction.

Applicants invite the Examiner's attention to Herlyn at page 1439, second column, second paragraph, which states that "Cells of the colorectal carcinoma line SW-480 did not bind antibodies secreted by the two hybridomas and their clones." To show that the presently claimed antibodies are distinct from those of Herlyn, Applicants invite the Examiner's attention to Table 1 of U.S. Patent No. 5,688,657, at column 23, which shows that monoclonal antibodies 31.1 and 33.28 both react with colorectal carcinoma cell line SW-480.

In view of this distinction, the disclosure of Herlyn does not anticipate the claims. Accordingly, the rejection should be withdrawn.

B. By Hollinshead

Claims 5-6, 23, 51-52 are rejected under 35 U.S.C. §102(b) as being anticipated by Hollinshead et al., 1985, Cancer 56:480-489 ("Hollinshead").

The Examiner states that Hollinshead discloses a monoclonal antibody to a colon carcinoma antigen having a molecular weight of 72 kilodaltons which is not present in normal tissue. "It is the Examiner's position that Hollinshead et al. have produced hybridomas which secrete antibodies that are directed to the same antigen that the claimed antibodies bind."

To serve as prior art against the claims, a reference must be enabling. Hollinshead does not disclose any hybridoma with sufficient detail to enable a person to either produce the hybridoma itself or to characterize the monoclonal antibody produced by it. Hollinshead discloses that the monoclonal antibodies are produced using "monoclonal antibodies produced by human-human hybridomas using splenocytes from a TAA-immunized patient donor," as described by reference 11, a manuscript in preparation. TAAs according to Hollinshead consist "of two fairly stable polypeptides, with approximate molecular weights of 72,000 d and 88,000 d, that are associated with colon carcinoma." This is not sufficient disclosure to enable a skilled artisan to make and use the monoclonal antibodies described in Hollinshead, let alone the antibodies produced according to the present invention using murine-derived hybridomas.

As regards claims 51 and 52, it should be noted that access to monoclonal antibody 31.1 allows for a purification of antigen which is not enabled by Hollinshead, which does not provide an enabling disclosure of any monoclonal antibody which can be so used. To more clearly set forth this distinction, claim 51 has been amended to refer to a "purified antibody which is raised against an immunopurified human colon carcinoma associated antigen," as supported by the original patent at column 21 lines 3-11. This amendment is acknowledged in the Supplementary Reissue Declaration by Assignee.

Therefore, none of the claims are anticipated and it is requested that the rejection be withdrawn.

5. The Claims Are Not Obvious

A. Over Hollinshead and Neuberger

Claims 5-15, 23, 30-33 and 51-52 are rejected as obvious over Hollinshead and further in view of Neuberger. According to the Examiner:

> One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have labeled the antibody in view of Hollinshead et al. and Neuberger et al. because Hollinshead et al. teach the antigen is of molecular weight 72 kd and the antigen is a colon carcinoma associated antigen and an ELISA for detection of the antigen was performed and the antibody was labeled with an enzyme. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have labeled the antibody in view of Hollinshead et al. and Neuberger et al. because Neuberger et al. teach labeling of antibodies for detection and treatment with cytotoxic agents and radiolabels of antibodies. Thus, it would have been obvious to one of ordinary skill in the art to produce an antibody which is a labeled antibody to the antigen of Hollinshead in view of Neuberger et al.

Applicants assert that the claims are not obvious over Hollinshead in view of Neuberger. As set forth above, Hollinshead is not enabling as regards any monoclonal antibody, and as such it does not provide sufficient disclosure to create any reasonable expectation of success in achieving the claimed invention. Neuberger does not supply any of the deficiencies of Hollinshead. Therefore neither reference, nor their combination, renders the claimed invention obvious, so that the rejection should be withdrawn.

B. Over Herlyn and Koprowski In View Of Neuberger

Claims 5, 7-15, 23, 30-33 and 51-52 are rejected under 35 U.S.C. §103(a) as obvious over Herlyn as evidenced by Koprowski and further in view of Neuberger. The Examiner contends that "it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have labeled the antibody in view of Herlyn et al. in view of Neuberger et al.."

For reasons set forth above, the antibodies of the present invention are distinct from the antibodies disclosed in Herlyn. Combining references Koprowski and Neuberger does not cure this deficiency of Herlyn. Therefore, none of the cited

references, nor any combination thereof, can render the claims obvious, so that the rejection should be withdrawn.

CONCLUSION

For all the foregoing reasons, the rejections should be removed and the claims should be allowed to issue.

Dated:

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